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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,002	05/20/2005	Ugur Sahin	4883-0001	7473

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MORGAN & FINNEGAN, L.L.P.
3 WORLD FINANCIAL CENTER
NEW YORK, NY 10281-2101

EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
02/14/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTOPatentCommunications@Morganfinnegan.com
Shopkins@Morganfinnegan.com
jmedina@Morganfinnegan.com

Office Action Summary	Application No.	Applicant(s)	
	10/537,002	SAHIN ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *99-104 and 107-115* is/are pending in the application.

4a) Of the above claim(s) *107-115* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *99-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/27/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 27, 2007 has been entered.

2. An action on the RCE follows.

3. Claims 99-104 and 107-115 are currently pending, claims 107-115 have been previously withdrawn by the Examiner. Applicants have amended claims 99-104.

4. The following rejections are being maintained:

Priority

5. Applicants argue that the instant application should be granted a priority date of at least November 21, 2003. The instant application is a national phase application under 35 U.S.C. §371 of International Application No. PCT/EP2003/013091. The applicants have claimed the benefit of the PCT application in their oath/declaration filed on May 20, 2005, and the applicants assert that the instant application, as well as the international application provide enabling disclosures of the instant claims. Applicants argue that the Examiner alleges that Application No. PCT/EP2003/013091 was not published in English and thus allegedly does not meet the requirements of PCT article 11 (See Office Action of June 27, 2007, page 3). The applicants respectfully disagree with the Examiner's contentions. The applicants respectfully direct the Examiner's attention to 35 U.S.C. §365, 35 U.S.C. §371, and PCT Article 11, which do not require that the international application be submitted in English, but require that the PCT

application be filed "in the prescribed language" (See PCT Article 11(1)(ii)). The international application was filed in the European Patent Office, which allows applications to be filed in German. In accordance with 35 U.S.C. §371(c)(2), applicants have submitted to the PTO "a translation into the English language of the international application" at the time of the National Stage entry, on May 20, 2005. Applicants argue that the instant application be granted a granted a priority date of November 21, 2003 Applicants argue that they amended the instant specification on May 20, 2005, to add a new paragraph to include the priority information.

Applicants' arguments have been considered and have been found persuasive for setting a priority date of November 21, 2003 for the instant Application, but not for priority to the German Application No. 102 54 601.0 for the reasons previously set forth in the Office Action of June 27, 2007, section 4, pages 2-3.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 99-104 remain rejected under 35 USC 112 as lacking enablement for the reasons previously set forth on pages 16-22, section 13 of the Office Action of October 17, 2006 and on pages 3-4, section 5 of the Office Action of June 27, 2007.

Applicants argue that the Examiner has admitted that, "the specification is enabling for diagnosing stomach cancers and lung cancers by detecting the expression of Claudin-18A2 protein..." *(See,* page 4 of the Office Action dated June 27, 2007). The applicants agree. Applicants argue that diagnosing pancreatic and/or esophageal cancer is also enabled by the

instant specification because the methodology for diagnosing these cancers would be the same as the methodology used for diagnosing stomach and lung cancers. Table 3A of the application as filed (also, "Tabelle 3A" on p. 74 of the published PCT application WO 2004/047863) shows thatClaudin-18A2 is overexpressed in pancreatic and esophageal cancers, similar to stomach and lung cancers. Applicants argue that thus, diagnosing pancreatic and esophageal cancers is also enabled by the instant specification and claims as filed.

Applicant's arguments have been fully considered and have not been found persuasive because, although the same methods would be used for detecting the protein in different cancers, given the lack of a predictable correlation of mRNA and protein expression and the heterogeneity of cancer phenotypes, as previously set forth, it cannot be predicted that the expression of Claudin-18A2 mRNA express in pancreatic and esophageal cancers predictably correlates with Claudin-18A2 protein/SEQ ID NO: 16 expression in the absence of empirical evidence showing that Claudin-18A2 protein/SEQ ID NO: 16 is expressed in pancreatic and esophageal cancers.

Additionally, upon review and reconsideration, the claims are not enabled for a method of diagnosing stomach cancer by detecting Claudin-18A2 in a biological sample isolated from a patient in an amount greater than an amount of Claudin-18A2 in a normal biological sample because, as set forth in the 3rd paragraph of page 19 of the Office Action of October 17, 2006, because there is no increase in Claudin-18A2 protein in stomach cancer, just a change in the glycosylation status of Claudin-18A2, and there appears to be a decrease in the Claudin-18A2 protein level in stomach cancer compared to normal stomach, see Figure 30 of this Application or parental application WO 2004/047863. Additionally, Sanda et al. (J. Pathology 2006,

208:633-642) teach that in examining gastric cancer for Claudin-18 protein expression, that of the 20 gastric adenomas analyzed, 90% showed a decrease in Claudin 18 expression, see Abstract, p. 637, left col., Figure 4, Tables 3 and 4. The expression of Claudin 18 was detected with an antibody that recognizes the C-terminus of claudin 18 (see p. 634, right col., 2nd to last line), which would recognize both Claudin 18A1 and A2, which differ in the N-terminus, see p. 94, lines 19-20 of the instant specification and Figure 2 of Sanda et al.. However, Sanda et al. did not detect any claudin 18A1 mRNA in any of their gastric cancer samples using RT-PCR, see figure 3B, variant 1. Thus, the detected Claudin18 protein levels in gastric cancer are predictably those of Claudin 18A2. Given that neither the art nor the instant specification detect Claudin 18A2 in a greater amount in a stomach cancer versus normal tissue, and rather Claudin 18A2 is detected in lesser amounts compared to normal stomach tissue, one of skill in the art could not predictably use the claimed method for diagnosing stomach cancer without undue experimentation.

Applicants argue that the Examiner is of the opinion that Table 3 of the instant specification is drawn only to mRNA expression in the pancreas and esophageal cancer and that there is no predictable correlation between mRNA levels and protein levels (Advisory Action, page 2, paragraph 2). Applicants respectfully disagree with the Examiner's contention. Applicants respectfully direct the Examiner's attention to the instant specification which shows that increased mRNA expression of lung cancer *(See,* Table 3 and Figures 29-31) also correlates with increased Claudin-18A2 protein expression *(See,* page 98, lines25 - 29, and Figures 29-31 of the specification as filed). Applicants argue that of ordinary skill in the art would understand that the correlation between the increase in Claudin-18A2 mRNA expression with the increase in

Claudin-18A2 protein expression would be expected in all cancer types that overexpress Claudin-18A2 mRNA *(i.e.,* the correlation would not be unique to lung cancer alone). Applicants argue that diagnosing pancreatic and esophageal cancers is also enabled by the instant specification and claims as filed because there is a correlation between increased mRNA expression and increased protein expression of Claudin-18A2 in pancreatic and esophageal cancers.

Applicant's arguments have been fully considered and have not been found persuasive becauseof the lack of a predictable correlation of mRNA and protein expression and the heterogeneity of cancer phenotypes, as previously set forth, it cannot be predicted that the expression of Claudin-18A2 mRNA express in pancreatic and esophageal cancers predictably correlates with protein expression based only the expression of Claudin-18A2 mRNA and protein in lung cancer of in the absence of empirical evidence showing that Claudin-18A2 protein/SEQ ID NO: 16 is expressed in pancreatic and esophageal cancers. Additionally, Table 3 of the foreign priority docoment, German Application No. 102 54 601.0, page 58 of the original document and page 68 of the translated document, shows the level of expression of claudin 18A2.1 mRNA to be the same in pancreatic cancers and normal pancreatic tissue. Thus, it is unclear based on the teachings of the specification and priority documents if there are even changes in claudin 18A2.1 at the mRNA level in pancreatic cancer. Thus, even if it were found that mRNA levels correlated with protein levels, one of skill in the art would not predictably expect to diagnose pancreatic cancer based on the level of SEQ ID NO: 16 (claudin 18A2.1) given that it is unclear whether or not even if the mRNA encoding SEQ ID NO: 16 is increased in pancreatic cancer.

Applicant's arguments have not been found persuasive and the rejection is maintained.

New Grounds of Objection/Rejection

Specification

7. The specification is objected to for improper disclosure of amino acid sequences without a respective sequence identifier, i.e. SEQ ID NOs:, see p. 67, lines 31- 32, p.68, lines 20-35, p.69, lines 1-31. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d). *Failure to supply the appropriate sequences identification numbers in response to this action will be considered non-responsive.*

Claim Rejections - 35 USC § 112

8. Claims 99, 100 and 102-104 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 100, 102-104 embody the method of claim 99 wherein an agent which binds specifically to a tumor associated antigen of SEQ ID NO:16 is used for the detection of said tumor associated antigen. Claim 99 lacks any limitation of the means by which the tumor associated antigen is detected. The instant method claims are thus reliant on the identity of a genus of binding agents. The specification describes only antibodies as the agents which can bind. When given the broadest reasonable interpretation, the term "agent" encompasses any type of compound, protein or non-protein such as a small organic molecule, a carbohydrate or

polysaccharide, that can bind to a tumor-associated antigen which is the protein of SEQ ID NO:16, therefore the genus of binding agents is highly variant encompassing compounds which vary significantly both in structure and function from each other. The description of antibodies as specific binding agents fails to adequately describe the genus of agents because said genus tolerates members which differ significantly in both structure and function from that of antibodies that bind to SEQ ID NO:16. One of skill in the art can reasonably conclude that applicant was not in possession of a genus of "binding agents" at the time the invention was filed. Because the genus of "binding agents" is not adequately described, the method claims relaying on said genus are also not adequately described.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in

the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

In the instant case the geus is only described as a definition by function (i.e. binding to SEQ ID NO:16) and beyond that of an antibody, one of skill in the art cannot readily visualize or recognize the identity of members of the genus.

9. All other objections and rejections recited in the Office Action of June 27, 2007 are withdrawn.

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PETER J. REDDIG whose telephone number is (571)272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Examiner, Art Unit 1642

/Karen A Canella/

Ph.D., Primary Examiner,

Art Unit 1643

PJR